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Response to Argument

UNITED STATES DEPARTMENT OF COMMERCE

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Washington, D.C. 20231

**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Paper No. 25

Application Number: 08/644289

Filing Date: 05/10/96

Appellant(s): Molly F. Kulesz-Martin

Michael L. Dunn
For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed 08/01/2000.

(1) *Real Party in Interest*

A statement identifying the real party in interest is contained in the brief.

(2) *Related Appeals and Interferences*

The brief does not contain a statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief. Therefore, it is presumed that there are none. The

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Board, however, may exercise its discretion to require an explicit statement as to the existence of any related appeals and interferences.

(3) *Status of Claims*

The statement of the status of the claims contained in the brief is correct.

(4) *Status of Amendments After Final*

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) *Summary of Invention*

The summary of invention contained in the brief is correct.

(6) *Issues*

The appellant's statement of the issues in the brief is substantially correct. The changes are as follows: Claims 16 and 19 are no longer an issue under 35 USC 112 second and first paragraph.

(7) *Grouping of Claims*

The appellant's statement in the brief that certain claims do not stand or fall together is not agreed with because the claims are not drawn to patentably distinct inventions, and have been subjected to the same or related art rejections.

(8) *ClaimsAppealed*

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) *Prior Art of Record*

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The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

Harris et al. "Structure and function of the p53 tumor suppressor gene: Clues for rational cancer therapeutic strategies". J. Natl Cancer Inst, vol 88, no. 20 (October 16, 1996), pp. 1442-1455.

Han et al. "Alternatively spliced p53 RNA in transformed and normal cells of different tissue types." Nucleic acid Res, vol 20, no. 8 (April 25, 1992), pp. 1979-1981.

Sambrook et al (eds). Molecular Cloning, A laboratory Manual. Second Edition, (Cold Spring Harbor Laboratory Press. 1989), p. 17.2.

EP, A1, 0 529 160 LEE et al 03-03-93.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

1.A. Claims 1, 3-6, 8-11, 15, 17 and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Appellant regards as the invention.

Claims 1, 3-6, 8-11, 15, 17 and 18 are indefinite because the language "active wild type p53" found in claims 1 and 5 does not set forth the metes and bounds of the patent protection desired. It is not clear which activity of wild type p53 that the claimed p53as has

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equivalent function with, and in which conditions wherein wild type p53 is active, in view of the fact that active wild type p53 has a multitude of functional activity, and that p53as is different from p53, and accumulates in G2, instead of G1, phase of cell cycle, wherein said difference in properties are suggestive of cellular functions distinct from p53 (specification, p.1, 2nd paragraph, lines 14-19), and further in view of the fact that activity of p53 is dependent on certain conditions (Harris et al).

B. Claims 1, 3-6, 8-11, 17 and 18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is a new matter rejection.

Claims 1, 3-6, 8-11, 17 and 18 are drawn to a plasmid or viral vector containing a cDNA sequence which encodes a protein designated p53as. Said p53as is functionally equivalent in growth regulation to active wild type p53, and is sequentially the same up to the final 50 carboxy terminal amino acids of p53. Said p53as is different from p53 within the final 50 carboxy terminal amino acids of p53 so as to lack a negative regulatory domain of p53, and so as to provide an epitope within said p53as which gives rise to an antibody which is specific for p53as protein only. In other words, said epitope is unique and is not only different from p53, but also different from any other proteins, and said epitope could be anywhere within p53as.

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The specification does not contemplate nor discloses adding a unique epitope to anywhere within said p53sa. The specification discloses an alternatively spliced p53 molecule which is distinguished from wild type p53 in its C-terminal region. The alternatively spliced molecule is taught to lack the negative regulatory region, and have 17 unique amino acids from intron 10. The specification further discloses substitution within the last 50 amino acids of wild type p53 to obtain p53sa (p.3). Nowhere in the specification does one find the contemplation or disclosure of incorporating, i.e. adding or providing, a unique epitope to p53sa, i.e. an epitope which is different not only from p53 but also any other proteins. There is no contemplation or disclosure of the structure or composition of the added unique epitope. Thus although the concept of substitution within the last 50 amino acids of wild type p53, or the concept of non-p53 sequences at the terminal end, is disclosed in the specification, the concept of substitution within the last 50 amino acids of wild type p53, so as the non-p53 amino acids would provide a unique epitope for p53sa, i.e. an epitope different not only from p53 but also any other proteins, is not supported by the specification. In other words, **contemplation of making or using non-p53 sequences at the terminal end for the purpose of providing a unique epitope for p53sa, which is different from not only p53, but any other proteins, is not supported by the specification.** Furthermore, although substitution of amino acids within the last 50 amino acids of wild type p53 is supported by the specification, the location of the claimed epitope, i.e. anywhere within p53sa, is not supported by the specification.

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C. Claims 1, 3, 4, and 17 are rejected under 35 USC 103(a) as being unpatentable over Han et al, in view of Sambrook et al.

Claims 1, 3, 4, and 17 are drawn to a plasmid containing a cDNA sequence which encodes a protein designated p53as. Said p53as is functionally equivalent in growth regulation to active wild type p53, and is sequentially the same up to the final 50 carboxy terminal amino acids of p53. Said p53as is different from p53 within the final 50 carboxy terminal amino acids of p53 so as to lack a negative regulatory domain of p53, and so as to provide an epitope within said p53as which gives rise to an antibody which is specific for p53as protein only. Said p53as naturally occurs in a mammal, or more specifically in a mouse. Claims 1, 3, 4, and 17 are further drawn to a cell transfected with said plasmid.

Han et al teach making of cDNAs from alternatively spliced p53 RNA in transformed and normal murine epidermal cells, using reverse transcriptase. Han et al further teach using polymerase chain reaction, and specific primers to amplify fragments from said cDNA, which are cloned into plasmids for sequencing. Han et al also teach that sequence analysis of the plasmids show regions representing regularly spliced wild type p53, and alternative splicing at the 3' end of intron 10. The alternatively spliced species AS-p53 are predicted to result in premature termination of p53 protein, making it 9 amino acid shorter and differing in 25 amino acids at the C-terminus. Otherwise, the molecule is identical to wild type p53 (See the abstract, p.1980, column 2, last paragraph to p.1981, column 1, first paragraph and third paragraph). Thus the existence of alternatively spliced RNA of p53 taught by Han et al meets

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the requirement of the instant p53sa, i.e. C-terminal truncation of 9 amino acids, and difference from p53 by 17 amino acids from intron 10. Han et al further teach that “more precise biochemical and **biological characterization** of AS-p53 protein along with R-p53 protein appear to be critical in future studies of p53 function in normal cells and in oncogenesis” (p.1981, column 2, first paragraph).

Han et al do not teach a plasmid containing full length p53as cDNA, and a cell transformed with said plasmid.

Sambrook et al teach that expressing large amounts of proteins from cloned genes in plasmids is an art standard technique, and is valuable to the purification, localization, and functional analysis of the proteins. Sambrook et al also teach intact native proteins have been produced in large amount in *E. Coli* for functional studies (p. 17.2, lines 10-11). Thus a host cell, i.e. *E. Coli*, transfected with a plasmid for expressing intact proteins is taught by Sambrook et al.

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the invention was made to clone a full length p53as cDNA into plasmid for the following reasons: 1) To study function of a protein, i.e. p53 and AS-p53, as suggested by Han et al, it is art standard to obtain full length protein, because it is well known in the art that fragments of a protein usually would not have biological activity, as evidenced by Sambrook et al, who also teach that for functional study, large amount of **intact native protein** are produced. Furthermore, the full length p53as protein could be readily obtained by routine techniques of

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cloning and expressing a plasmid containing a full length cDNA, for producing intact native protein, as taught by Sambrook et al, 2) The existence of a full length p53as cDNA is known from the teaching of Han et al, because Han et al teach its predicted protein, as being prematurely terminated as compared to p53 protein, and having 9 amino acid shorter and differing in 25 amino acids at the C-terminus, as compared to p53 protein. Furthermore, although Han et al do not directly teach the structure of a full length p53as cDNA, one of ordinary skill in the art could readily obtain it, in view of the available information concerning the alternative spliced site on wild type p53, the primers unique for p53as, and the source of RNA for the alternatively spliced RNA, as taught by Han et al. The motivation is obvious, i.e. to obtain full length protein expressed by plasmid containing full length p53as cDNA for studying the function of p53as, since it is critical to include p53as in the study of the function of p53, as suggested by Han et al. One of ordinary skill in the art would have been motivated to clone full length p53as cDNA into plasmid with a reasonable expectation of success.

D. Claims 5, 6, 8-11 and 18 are rejected under 35 USC 103(a) as being unpatentable over Han et al, in view of Lee et al.

Claims 5, 6, 8-11 and 18 are drawn to a viral vector containing a cDNA sequence which encodes a protein designated p53as. Said p53as is functionally equivalent in growth regulation to active wild type p53, and is sequentially the same up to the final 50 carboxy terminal amino acids of p53. Said p53as is different from p53 within the final 50 carboxy

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terminal amino acids of p53 so as to lack a negative regulatory domain of p53, and so as to provide an epitope within said p53as which gives rise to an antibody which is specific for p53as protein only. Said p53as naturally occurs in a mammal, or more specifically in a mouse.

Claims 5, 6, 8-11 and 18 are further drawn to a cell transfected with said viral vector.

The teaching of Han et al has been set forth.

Han et al do not teach a viral vector containing full length p53as cDNA, and a cell transformed with said viral vector.

Lee et al teach the use of baculovirus vectors delivered into insect cells to produce large quantities of protein. Lee et al teach the importance and advantages of a mechanism to obtain intact, biochemically active protein in large quantities to advance investigation of the properties of that protein (page 2, lines 40-45). Thus not only does Lee et al teach the technical feasibility of a reasonable expectation of success, Lee et al also teach a motivation to do so, i.e. to obtain large quantities of intact, biochemically active protein for investigation of the properties of the protein.

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the invention was made to use the baculovirus vector system of Lee et al, with a reasonable expectation of success, as a vector for expressing other tumor suppressor protein, such as the full length alternatively spliced p53 cDNA, which could be readily obtained, in view of the available information taught by Han et al, i.e. the alternative spliced site on wild type p53, the primers unique for p53as, and the source of RNA for the alternatively spliced RNA. The

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motivation is obvious, i.e. to study the properties of the protein, as suggested by Han et al, and Lee et al.

(11) *Response to Argument*

A. Appellant argues that there is clearly no ambiguity in the use of the word “active” in the claims 1, 3-6, 8-11, 15, 17, and 18, which have been rejected under 112, second paragraph.

Appellant argues that neither Harris, nor the reviewers of “Cell” journal which published the reference by Hupp et al, nor the magazine had any difficulty understanding the meaning of “active” p53 or its ‘function’. One of skill in the art knows a myriad of effect of p53. One skill in the art already knows that p53 has a terminal negative regulatory domain that can turn off many, if not all, of the growth regulating properties of p53 under certain conditions. One of skill in the art already knows that when the negative domain is removed, the growth regulating properties of p53 can no longer be turned off. The Examiner is referred to the references cited in the information disclosure statement, and especially the reference by Hupp et al, for examples of such known information.

The arguments have been fully considered but is not found convincing for the following reasons. The language “active” does not set forth the metes and bound of the patent protection desired, because it is not clear which activity of the wild type p53 that the claimed p53as has equivalent function with, and under which conditions wherein the wild type p53 is “active”. It is well known in the art that active wild type p53 has a multitude of functional activity, such as

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DNA binding, DNA repair, transcriptional activation, cellular transformation, cell cycle arrest and apoptosis (programmed cell death) (Harris et al, or examples in several references cited in the information disclosure statement). Harris et al also teach that the activity of p53 is dependent on certain conditions. One of ordinary skill in the art would have expected that the function of p53as would not be exactly the same as that of wild type p53, wherein the 50 carboxy terminal amino acids are substituted in p53as (specification p.3, first paragraph), because of the following reasons: 1) Different from p53, which is primarily found in G1 stage of cell cycle, p53as accumulates in G2 phase of cell cycle, and said difference in properties are suggestive of cellular functions distinct from p53, as admitted by Appellant (specification, p.1, 2nd paragraph, lines 14-19), 2) C-terminal basic residues have many important functions, such as influencing the secondary structure of p53, containing sites for RNA linkage or phosphorylation by casein kinase II, and being required for stable oligomer formation *in vitro* between normal and mutant p53 (Han et al, p.1981, first column, last paragraph), and 3) although the specification discloses that p53as has DNA binding activity, the actual functional activity of p53as in DNA repair, transcriptional activation, cellular transformation, cell cycle arrest and apoptosis (programmed cell death) is not disclosed in the specification, and is unpredictable, due to modification of the C-terminal basic residues. Although the specification considers making p53as, which lacks the terminal regulatory region of the C-terminus basic domain, the specification does not discloses the structure of the terminal regulatory region. It is not clear whether deletion of terminal regulatory region could effect other functions of the

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C-terminus basis domain, besides effecting negative regulation of p53, because it is unpredictable whether said terminal regulatory region overlaps with other regions within the C-terminus basis domain, which have many important functions.

B. Appellant argues that the rejection of claims 1, 3-6, 8-11, 17 and 18 under 35 USC 112, first paragraph, as containing subject matter not sufficiently described in the specification, i.e. new matter, should be reversed. Appellant argues that the desirability of incorporating a unique epitope is taught in the specification. Appellant argues that in view of the discovery by the inventor of terminally modified p53 that cannot be turned off (p53as) having a terminal sequence that raises a unique antibody, the inventor concluded that p53 could be easily truncated to remove the negative regulatory domain, and a large number of different terminal sequences could be substituted that raise unique antibodies. Appellant argues that the specification on page 2, last paragraph recites synthetic p53as having terminal amino acids different from the 50 terminal amino acids of p53, and thus clearly contemplates non-p53 sequences at the terminal end. Appellant further argues that attaching a unique epitopes to proteins and peptides are routine in the art.

The arguments have been fully considered but is not found convincing for the following reasons. The issue here is not whether one of skill in the art could attach a unique epitope to p53as. The issue here is whether contemplating of making or using a non-p53 sequence for the purpose of providing a unique epitope at anywhere within p53as is disclosed in the specification. Although the concept of substitution within the last 50 amino acids of wild type

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p53 is disclosed in the specification, the concept of substitution within the last 50 amino acids of wild type p53 so as to provide a unique epitope for p53sa, which is different from not only p53, but any other proteins, is not supported by the specification. In other words, contemplation of making or using non-p53 sequences at the terminal end for the purpose of providing a unique epitope for p53sa, which is different from not only p53, but any other proteins, is not supported by the specification. Furthermore, although substitution of amino acids within the last 50 amino acids of wild type p53 is supported by the specification, the location of the claimed epitope, i.e. anywhere within p53sa, is not supported by the specification.

C. Appellant argues that the rejection of claims 1, 3, 4 and 17 under 35 USC 103 over Han et al in view of Sambrook et al is improper and should be reversed. Appellant argues that the rejection is based on hindsight. Appellant argues that Han et al only interest in sequencing and thus teach against incorporating an entire p53as cDNA sequence, because it is difficult to sequence large DNA fragments. Han et al give no reason to expect, nor suggest that incorporation of a whole p53 would somehow further the study of function or be useful for such a purpose. Appellant argues that combining Han et al and Sambrook et al accomplish nothing. A generic teaching of a large amount of protein is not equivalent to saying that long sequences can or should be incorporated into plasmids. Large amount of protein and long sequences are not the same thing or even similar.

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The arguments have been fully considered but is not found convincing for the following reasons. To study function of a protein, i.e. p53 and AS-p53, as suggested by Han et al, it is art standard to obtain full length protein, because it is well known in the art that fragments of a protein usually would not have biological activity. Moreover, Sambrook et al also teach that for functional studies, intact native proteins have been produced in large amount (p. 17.2, lines 10-11). Furthermore, the full length p53as protein could be readily obtained by routine techniques of cloning and expressing a plasmid containing a full length cDNA, as taught by Sambrook et al, wherein the existence of full length p53as RNA is known in the art, as taught by Han et al, and its full length cDNA could be readily obtained, *supra*. Thus the arguments that large amount of protein and long sequences are not the same thing or even similar are rendered moot, in view of the teaching of Sambrook et al that intact native proteins have been produced in large amount for functional studies.

Moreover, In re Kerkhoven (205 USPQ 1069, CCPA 1980) summarizes:

"It is prima facie obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose: idea of combining them flows logically from their having been individually taught in prior art." Neither Han et al nor Sambrook et al teach a plasmid containing full length p53as. However, in the absence of unexpected results, it would have been prima facie obvious to one of ordinary skill in the art to combine the teachings of the references and to incorporate a full length cDNA p53as into a plasmid for producing full length p53as protein

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for the same purpose of studying function of the expressed protein. The instant situation is amenable to the type of analysis set forth in In re Kerkhoven, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to for a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant claims, given the teaching of the prior art of the existence of full length p53as RNA, wherein its full length cDNA could be readily obtained, and of the importance of studying its function, in view of the teaching of the routine use of plasmid for expressing intact protein for studying its function, it would have been obvious to incorporate full length cDNA p53as into a plasmid, because the idea of doing so would have logically followed from their having been individually taught in the prior art to be useful for producing large amount of intact protein for studying its function. One of ordinary skill in the art would have expected to obtain plasmids containing full length cDNA p53as with a reasonable expectation of success.

D. Appellant argues that the rejection of claims 5, 6, 8-11 and 18 under 35 USC 103 over Han et al in view of Lee et al is similarly flawed hindsight combination. Neither references suggests incorporating p53as into anything; therefore their combination certainly makes no such suggestion.

The arguments have been fully considered but is not found convincing for the following reasons. To study function of a protein, i.e. p53 and AS-p53, as suggested by Han et al, it is

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art standard to obtain full length protein, because it is well known in the art that fragments of a protein usually would not have biological activity. Moreover, Lee et al teach the importance and advantages of using viral vectors to obtain intact, biochemically active protein in large quantities to advance investigation of the properties of that protein.

Moreover, .In re Kerkhoven (205 USPQ 1069, CCPA 1980) summarizes:

"It is prima facie obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose: idea of combining them flows logically from their having been individually taught in prior art." Neither Han et al nor Lee et al teach a viral vector containing full length p53as. However, in the absence of unexpected results, it would have been prima facie obvious to one of ordinary skill in the art to combine the teachings of the references and to incorporate a full length cDNA p53as into a viral for producing full length p53as protein for the same purpose of studying function or properties of the expressed protein. The instant situation is amenable to the type of analysis set forth in In re Kerkhoven,205 USPQ 1069 (CCPA 1980) wherein the court held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to for a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant claims, given the teaching of the prior art of the existence of full length p53as RNA, wherein its full length cDNA could be readily obtained, and of the importance of

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studying its function, in view of the teaching of the routine use of viral vectors for expressing intact protein for studying its function or properties, it would have been obvious to incorporate full length cDNA p53as into a viral vector, because the idea of doing so would have logically followed from their having been individually taught in the prior art to be useful for producing large amount of intact protein for studying its function or properties. One of ordinary skill in the art would have expected to obtain a viral vector containing full length cDNA p53as with a reasonable expectation of success.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Minh-Tam Davis, PhD.
October 8, 2000

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